Prehypertension:
To treat or not to treat

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Definition:
Blood pressure from 120-139 systolic
  80-89 diastolic

Importance:
Starting point in CVD continuum
↓ Life expectancy by 5 years
TROPHY trial

• Trial of preventing hypertension.
• Hypothesis:
  ↓ RAS in pre-hypertensive → interferes with self accelerating process leading to HTN and end organ damage.

• Patients and methods:
  777 patients with prehypertension.
  Treated for 2 years with either candesartan or placebo.
  Another 2 years of placebo in both groups.
• Endpoint:
  Development of stage I hypertension.
Results
(2 years after ttt was stopped)

• HTN observed less frequently in candesartan group.
• Significant absolute difference of 9.8%.
• RRR of 15.6% to develop HTN after 4 years.
• Slightly lower BP readings.
• Fewer use of therapy in the CG.

Conclusion

Administering ARBs for 2 years postponed the manifestation of stage I HTN for a prolonged period.

• Clinical implications:
Pre-HTN BP and the involved RAS → are key players in the vicious circle leading to HTN.
Results should be interpreted with caution

• The need of M.T. in prevention trial → define as HTN.
• Using the criteria of 3 average readings → HTN in all.
• Active treatment may delay the onset of endpoint.
• Placebo group needing treatment in y 1&2 and candesartan group needing treatment in y 3&4 are equal.

CONCLUSION:
Candesartan delayed but not prevented the onset of HTN.

Important Question

• Whether any T.O.D. can be prevented by drug treatment of pre-HTN??
• GL moves focus to → global risk.
• Most pre-HTN → have additional risk factors.
• ARIC study → pre-HTN have other R.F. ± obesity.
• Whether other R.F. → enhance benefit of M.T in pre-HTN.
• Pts with Pre-HTN and DM and CRF → data are clear.
• Pre-HTN and co-existing VD → MT improves organ protection.
Another important point from TROPHY study

• The rapid progression from pre-HTN to HTN
• Drug therapy
  → Organ protection
  → Changes the natural history of the disease
Current recommendation for the management of pre-HTN:
• Life style modification.
• Pharmaco-therapy ?? More convenient
  
  \textit{may be in certain high risk patient.}

Importance questions about M.T. of pre-HTN

• Who should be treated ?
• For how many years ?
• Which drugs and of what dose ?

For now a healthy lifestyle is the foundation for all therapies in persons with pre-HTN.
Framingham Heart Study concluded

High normal B.P. is associated with an ↑ risk of CVD (Hazard Ratio: 2.5 in females and 1.6 in males)

Baseline characteristics of the study subjects
Cumulative incidence of the 1\textsuperscript{st} CV event

**Table 2. Cumulative Incidence of a First Cardiovascular Event Among Study Subjects, According to Blood Pressure Category at Baseline.**

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>WOMEN</th>
<th>10-YR. CUMULATIVE INCIDENCE (95% CI)</th>
<th>MEN</th>
<th>10-YR. CUMULATIVE INCIDENCE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NO. OF EVENTS/ NO. AT RISK</td>
<td></td>
<td>NO. OF EVENTS/ NO. AT RISK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Crude Age-Adjusted</td>
<td>Crude Age-Adjusted</td>
<td>Crude Age-Adjusted</td>
<td>Crude Age-Adjusted</td>
</tr>
<tr>
<td>Optimal</td>
<td>26/1876</td>
<td>1.8 (0.8–1.8)</td>
<td>1.9 (1.1–2.7)</td>
<td>55/1005</td>
</tr>
<tr>
<td>Normal</td>
<td>99/1120</td>
<td>2.0 (1.9–3.0)</td>
<td>2.9 (1.9–4.8)</td>
<td>95/1029</td>
</tr>
<tr>
<td>High-normal</td>
<td>92/1811</td>
<td>1.4 (0.8–2.0)</td>
<td>4.4 (2.2–8.5)</td>
<td>100/993</td>
</tr>
</tbody>
</table>

*Optimal blood pressure is a systolic pressure of less than 120 mm Hg and a diastolic pressure of less than 80 mm Hg. Normal blood pressure is a systolic pressure of 120 to 129 mm Hg or a diastolic pressure of 80 to 84 mm Hg. High-normal blood pressure is a systolic pressure of 130 to 139 mm Hg or a diastolic pressure of 85 to 89 mm Hg. If the systolic and diastolic pressure readings for a subject were in different categories, the higher of the two categories was used. CI denotes confidence interval.

The numbers have been adjusted by direct standardization to the overall age distribution of the subjects in the study sample in four age groups (<50 years, 50 to 59 years, 60 to 69 years, and ≥70 years).

Cumulative incidence of the 1\textsuperscript{st} CV event
Results of sex-specific multivariable cox-proportional hazards regression model

<table>
<thead>
<tr>
<th>TYPE OF MODEL AND BLOOD-PRESSURE CATEGORY</th>
<th>HAZARD RATIO (95% CONFIDENCE INTERVAL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Models with blood pressure defined at base line</td>
<td></td>
</tr>
<tr>
<td>Optimal (3880 subjects)</td>
<td>1.0 (95% CI: 1.0-1.0)</td>
</tr>
<tr>
<td>Normal (2185 subjects)</td>
<td>1.5 (95% CI: 1.0-2.2)</td>
</tr>
<tr>
<td>High normal (2194 subjects)</td>
<td>2.5 (95% CI: 1.6-4.3)</td>
</tr>
<tr>
<td>P for trend across categories</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The recent WHO-ISH report

It emphasized the rational for expecting high-risk subjects without HTN to benefit from BP lowering and the need for clinical trials to investigate this possibility.
DEFINITIONS

• 1940 → Transient hypertension.
• 1970 → Borderline hypertension.
• 1990 → High normal BP.
• 2003 → Pre-hypertension.

Logistics of treating pre-HTN state

A) BP remains a strong predictor of CV events even in pre-HTN.

• HTN is a self-accelerating condition.
• Arteriolar hypertrophy, endothelial dysfunction, ↑ vaso-constriction and ↓ vasodilatation are described in pre-HTN.
B) Elevation in plasma norepinephrine and plasma renin concentration have been described in pre-HTN.

C) Absence of evidence of the long-term efficiency of lifestyle approaches.

Kaplan-Meier analysis of new-onset clinical HTN
Four participants with pre-HTN needed to be treated for 2 years to prevent one case of new onset HTN.

Hazard ratios for new onset HTN in various subgroups
BP in the two study groups

Diamonds = Candesartan group
Squares = Placebo group
Triangles = Difference between the two groups

In MRFIT trial participants with pre-HTN had age-adjusted relative risks of 1.61 and 2.14 for fatal coronary events and strokes respectively.
Although the observation in this study indicates that candesartan may ameliorate BP in persons with pre-HTN we do not advocate treatment of the 25 million pre-HTN.

*Again the issue of cost-effectiveness should be solved.*

It is recognized that the CV risk ↑ linearly at BP levels lower than those that usually trigger the use of anti-HTN therapy.
In the Framingham Heart Study, the risk of CVD in *patients with high normal BP* was higher than those with optimal BP.

The clustering of high normal BP with other risk factors may partially mediate the risk of high normal BP.
Why is high BP associated with ↑ rate of CV events?

A) The hemodynamic consequences.
B) Other mechanisms liking ↑ BP to premature atherosclerosis:
   - ↑ sympath. activity.
   - ↑ activity of the RAS.
   - Psychosocial factors.
C) Endothelial dysfunction leading to:
   - ↓ NO activity.  → Impaired endothelial dependant VD
   - ↑ endothelin 1.

Endothelial dysfunction with HTN
Important questions to be answered

• Should clinicians modify the BP threshold for the use of anti-HTN agents?
• If high-normal BP should be treated, should medications be used? → cost, side-effects.
• Role of global risk effect aside from high BP.

Criticisms to the TROPHY trial

• Treatment of pre-HTN ↓BP (taking medications) but it does not ↓CV events.
• Over-ttt of 60% of those with pre-HTN with the corresponding unnecessary costs.
• Treatment of pre-HTN would have a tremendous economic effect on public health care systems.

• The increasing incidence of HTN and CVD is directly related to changes in lifestyle and eating patterns.

There is overestimation of the incidence of HTN in the pre-HTN group → use of home BP measurement is more reliable.
• Very high incidence of progression to HTN 63% in the placebo group, only 37% of progression in the Framingham study → Recruitment error.
• Claim that HTN can be prevented in the elderly by treatment in the pre-HTN stage → not proved incidence of HTN in the young and elderly.

Thank You